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PATENT SPECIFICATION

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(54) 1,2,4,5-TETRAHYDRO-3H,3-BENZAZEPINES

(71) We, WALLACE & TIERNAN INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 91 South Harrison Street, City of East Orange, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to substituted 1,2,4,5-tetrahydro-3H,3-benzazepines.

The compounds of this invention are useful as agents for producing analgesia and thus relieving pain in animals. They are also useful as antagonists of narcotics such as morphine.

As used throughout the following description and claims, the term "lower" means a group containing from 1 to 5 carbon atoms.

According to the present invention there is provided a compound of the formula:



Formula I

- or the pharmaceutically acceptable addition salts thereof, wherein R is H, lower alkyl; dialkylamino-alkyl, lower alkyl containing 3-6 carbon atoms: aryl-C₁-C₂ alkyl; cycloalkyl-alkyl, for example 2-(1-adamantyl)-ethyl-(adamantyl moiety unsubstituted or substituted with NH₂, OH, OCH₃, halogen, alkyl); aryl-cycloalkyl-alkyl, propargyl; aryl-lower alkyl, the aryl group selected from phenyl, n-phenyl, nitrophenyl, aminophenyl, acylaminophenyl, methoxyphenyl, hydroxyphenyl, methylaminophenyl, ethylaminophenyl, or dimethylaminophenyl; a lower alkyl ester of hydroxyalkyl; a heterocyclic group, an alkyl group substituted by a heterocyclic ring (unsubstituted or substituted with one or more phenyl, hydroxyl or aryl groups), 2-phthalimidoethyl-(the phenyl moiety unsubstituted or substituted in any of the remaining positions with NH₂, OH, OCH₃, halogen, alkyl); 2-(2-isindolyl)-ethyl-(the phenyl moiety unsubstituted or

SEE CORRECTION SLIP ATTACHED

substituted in any of the remaining positions with NH_2 , OH , OCH_3 , halogen, alkyl); 2-[4-benzyl-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o*, *m*, or *p*-position with NH_2 , OH , OCH_3); 2-[4-phenyl-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o*, *m*, *p*-position with NH_2 , OH , OCH_3 , halogen, alkyl); 2-[4-(*o*-methylbenzyl)-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o*, *m*, or *p*-position with NH_2 , OH , OCH_3 , halogen, alkyl); R^1 is hydrogen and R^2 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl, or R^1 and R^2 are lower alkyl; R^3 is hydrogen or lower alkyl; R^4 and R^5 are hydrogen, lower alkyl, CH_2OCH_3 , hydroxy, pyridine carboxylic acid ester of hydroxy group, amino, lower alkyl, halogen or nitro; R^6 and R^7 are hydrogen, lower alkyl, phenyl or phenylalkyl; R^8 is hydrogen, lower alkyl, phenyl or phenylalkyl; provided that when R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are hydrogen and R is allyl, dialkylammoniumalkyl or unsubstituted heterocyclyl-alkyl, R^9 is hydroxyl; provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 is other than hydrogen when R is either hydrogen, lower alkyl, allyl or phenyl-lower alkyl; and that neither R^1 nor R^2 is 6-chloro when R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are hydrogen and provided that when R^1 and R^2 are methoxy, R is not hydrogen or methoxy.

In the following discussion of the process of the invention the symbols R through R^9 are to be regarded as defined as above unless there is a specific indication to the contrary in the discussion. The compounds of the invention wherein R is hydrogen may be prepared by treating a compound of the formula



Formula II

with a hydrogen halide in a polar solvent such as acetic acid, warming the resulting 2-amino-4-halobenzazepine with water to provide a cyclic imide of the formula



Formula III

and selectively reducing the carbonyl groups adjacent the imide group in the compound of Formula III.

Borane is a suitable reagent for use in reducing the carbonyl groups of the compound of Formula III.

The compounds of the invention wherein R is hydrogen may also be prepared by hydrogenating a compound of Formula II. The hydrogenation is preferably effected catalytically using Raney nickel catalyst.

The compounds of the invention wherein R is hydrogen and any of the substituents R^1 through R^9 are lower alkyl, phenyl or phenyl lower alkyl may be prepared by reacting an amine of the formula



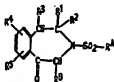
Formula IV

with a compound of the formula $\text{R}^6\text{-SO}_2\text{X}$ wherein R^6 is an organic radical and X is halogen, reacting the corresponding sulfonamide thus obtained with an ester of the formula



Formula V

wherein Alk is a hydrocarbon group and X is halogen, hydrolyzing the resulting ester, treating the acid thus obtained with a halogenating agent such as sulfonyl chloride to provide the corresponding acid halide, adding the acid halide to a cold suspension of aluminum trihalide to provide a benzazepinone of the formula



Formula VI

selectively reducing the carbonyl group in the azepine moiety of the compound of Formula VI and splitting off the radical R^4-SO_2- therefrom.

p-Toluenesulfonyl chloride is prepared for use as the compound of the formula R^4-SO_2X while ethylthiomacetate or appropriately substituted derivative thereof is preferred as the ester of Formula V.

Sodium borohydride is a preferred reagent for use in reducing selectively the carbonyl group in the compound of Formula VI.

The compounds of Formula I wherein R is other than hydrogen may be prepared by reacting such a compound in which R is hydrogen with a reagent which will replace the hydrogen with one of groups R other than hydrogen. Such reagents include compounds of the formulas RX and $R-C:OX$ wherein R is other than hydrogen and X is halogen, as well as aldehydes and ketones having at least three carbon atoms.

When a reagent of formula $R-C:OX$ is used the carbonyl moiety is subsequently selective reduced to a methylene group. Lithium aluminum hydride is a preferred reagent for the reduction.

When an aldehyde or ketone is used as the reagent the double bond in the moiety attached to the nitrogen atom in the azepine ring of the product may be reduced. Sodium borohydride is preferred for the reduction.

Suitable changes can be made in the substituents R^1 and R^2 in compounds of Formula I by means apparent to those skilled in the art. In one embodiment of the process of the invention, compounds of Formula I wherein R is hydrogen and at least one of R^1 and R^2 is an alkoxy group, are treated with aqueous hydrogen halide, preferably the bromide, to cleave the alkoxy group and provide a corresponding hydroxy group. The cleavage may be effected before or after the reaction of the compound of Formula I with compounds of formulas RX and $R-C:OX$ or an aldehyde or a ketone as discussed above.

Being organic bases the above compounds readily form salts with organic or inorganic acids such as hydrochloric, malic, tartaric, sulfuric, and other nontoxic acids to form pharmaceutically acceptable acid addition salts.

Particularly satisfactory compounds from the point of view of analgesic and narcotic antagonism are compounds in which R^1 and R^2 are hydroxy or lower alkoxy.

The following Reaction Scheme A illustrates graphically two general techniques for preparing a representative compound of Formula I wherein R is a hydrogen atom, one of R^1 and R^2 is a methoxy group and the other a hydrogen atom, substituents R^3 to R^5 and R^6 to R^8 being hydrogen.